

Outcomes in Congenital Hyperinsulinism: a Systematic Review

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Background

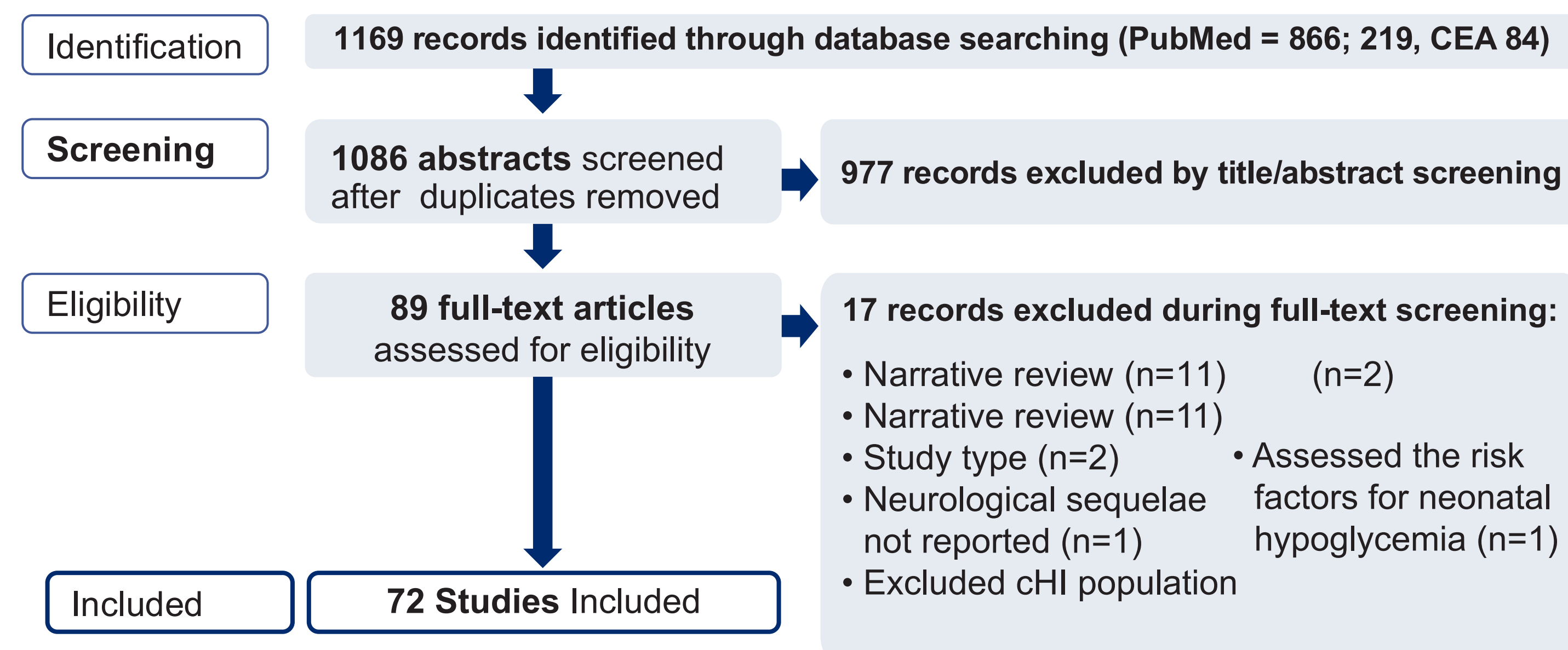
- Congenital hyperinsulinism (cHI) is the most common cause of persistent, severe hypoglycemia in newborns and infants and is associated with a high risk of hypoglycemic brain injury and long-term neurological sequelae.^{1,2}
- Despite medical management, a significant percentage of individuals with cHI still experience hypoglycemic episodes.³
- Evidence on disease progression, long-term outcomes, and treatment-related complications remains fragmented.^{2,4}

Objective

This exploratory systematic review addressed the research question: What is the extent and nature of hypoglycemic brain injury, neurological outcomes, and surgical complications in patients with cHI? In this way, we sought to provide an evidence base that would allow for more precise estimates of the neurological burden in cHI and aid in research prioritization and resource allocation.

Methods

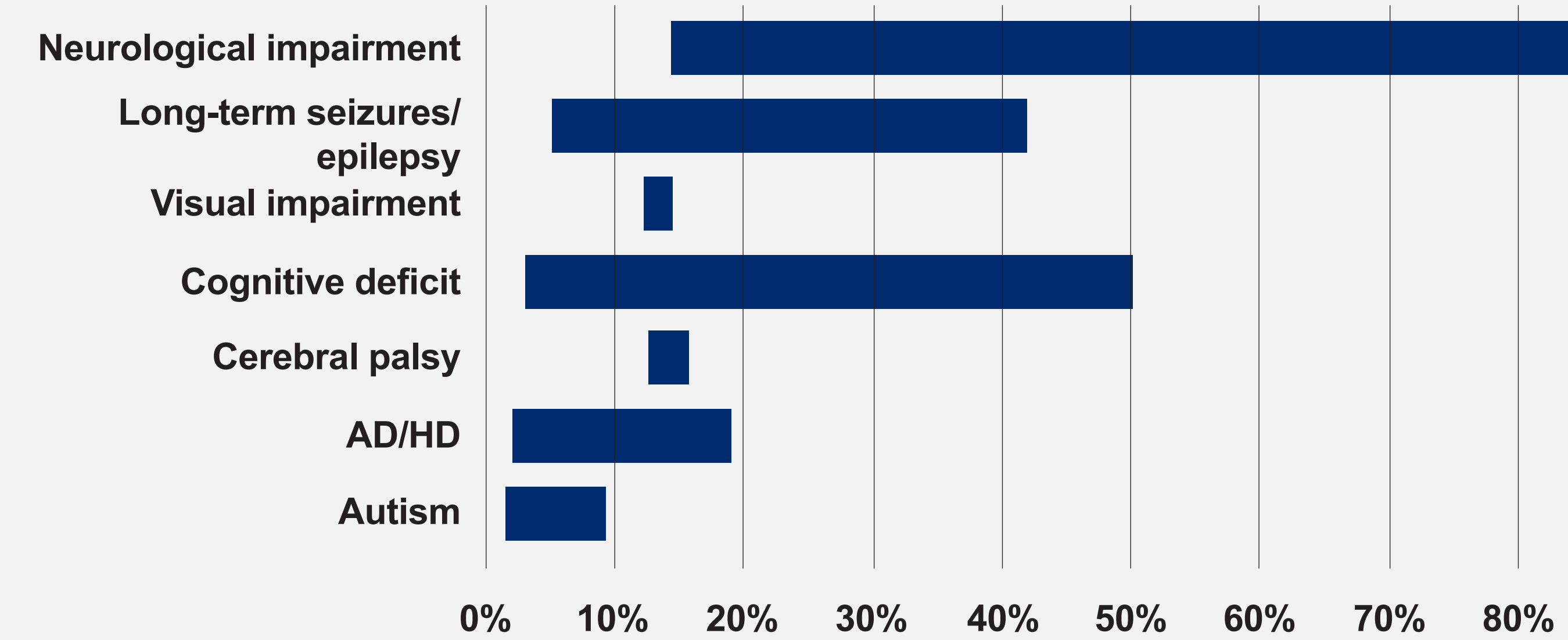
- A systematic literature search was conducted in PubMed and the Tufts Cost-Effectiveness Analysis (CEA) Registry for studies published in English between Jan. 2005 and May 2024.
- Abstracts and full texts were screened using predefined eligibility criteria, including populations with neonatal hypoglycemia or cHI; outcomes related to neurological sequelae, mortality, health-related quality of life (HRQoL), or cost of illness; and eligible study designs (observational studies, randomized controlled trials, and systematic reviews). Case reports (<5 patients) and non-systematic reviews were excluded.



Results

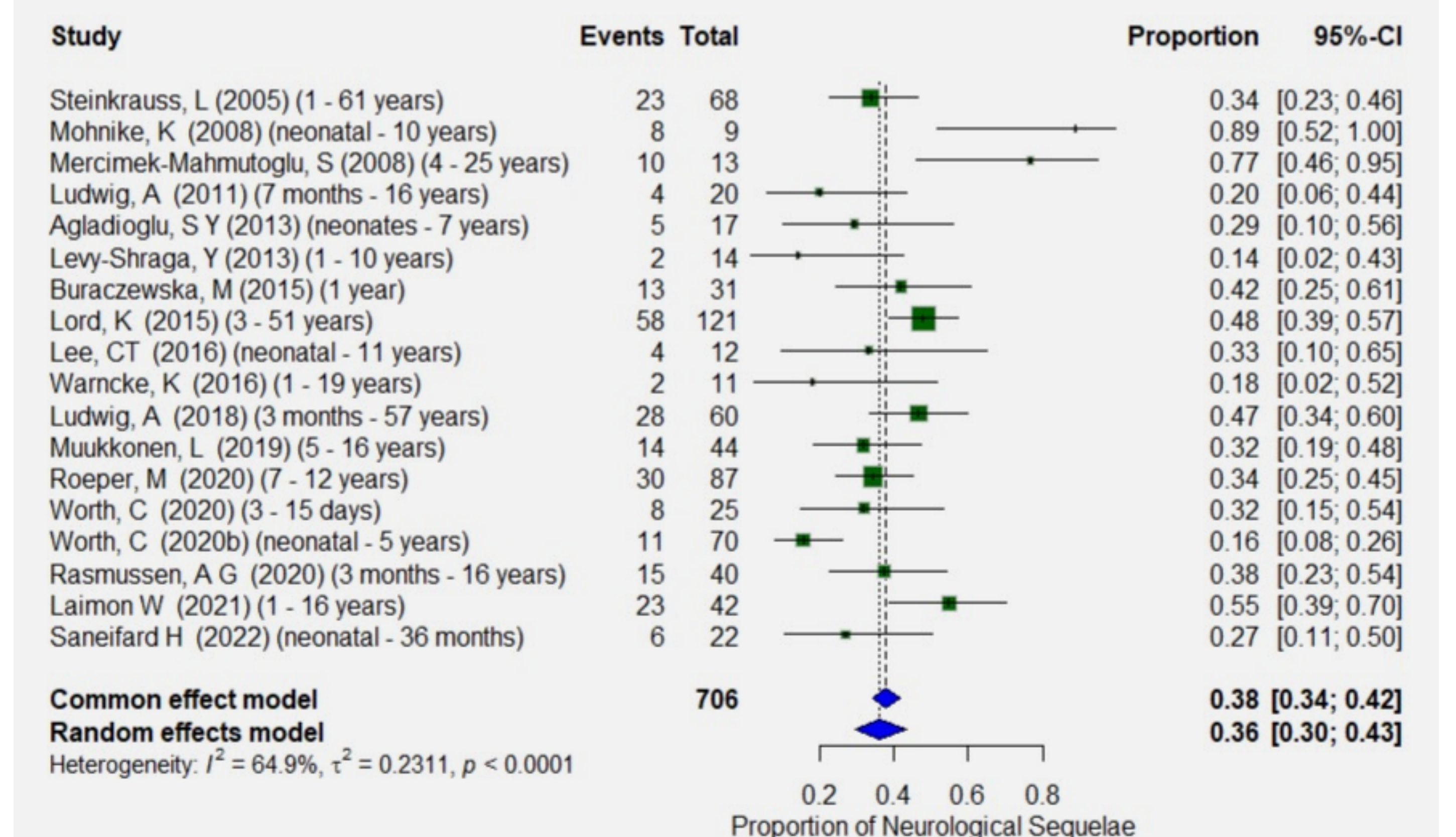
- We identified 72 studies: 47 on cHI and 25 on general hypoglycemia in neonates.
- Brain magnetic resonance imaging or electroencephalography revealed abnormal results in 11.8% to 88.9% of hypoglycemic patients.
- Neurological impairment in cHI patients ranged between 14.3% and 88.9%, with follow-up periods up to 25.5 years. cHI patients suffered from long-term seizures/epilepsy (5.0%-41.9%), visual impairment (11%-13%), cognitive deficit (3.0%-50.0%), and cerebral palsy (12.5%-15.4%). Attention-deficit/hyperactivity disorder (3.0%-20.0%) and autism (1.4%-9.4%) were also reported. (Figure 2)
- Delayed diagnosis increased risks of severe brain injury and/or neurological sequelae.
- Mortality ranged from 2.0-27.0%, often confounded by treatment complications.

Figure 2. Percentage range of cHI patients affected by different neurological sequelae across 72 studies



- The forest plot shows that across eighteen studies (706 participants), the pooled cumulative proportion of neurological sequelae was 38% (95% CI: 34-42%), with substantial heterogeneity ($I^2 = 64.9%$), indicating that neurological outcomes are common, but estimates vary significantly between studies (Figure 3).

Figure 3. Forest plot showing the proportion of neurological sequelae across 18 studies



- Pancreatectomy was frequently curative in focal cHI (up to 97%); however, outcomes were substantially less favorable in diffuse cHI (<50%), which was associated with higher rates of repeat surgery (4.0-22.0%), perioperative complications (3.0-5.0%), and a high long-term risk of diabetes mellitus, exceeding 90% at follow-up.

Key Takeaways

- Current evidence on cHI-related neonatal hypoglycemia, brain damage and subsequent long-term neurological sequelae is limited and heterogeneous.
- Pancreatectomy carries significant risks, including high rates of diabetes.
- Evidence on HRQoL and cost of illness in cHI is notably scarce, highlighting important gaps for future research.